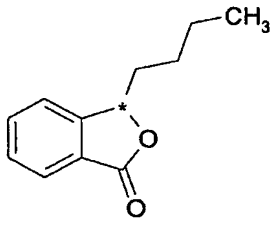
BUTYLPHTHALIDE SOFT GEL CAPSULE AND ITS PREPARATION PROCEDURE

Technical Field

[0001] This invention relates to a novel dosage form of butylphthalide soft gel capsules and its preparation.

Background Art

[0002] Butylphthalide is a major ingredient of celery (*Apium graveolens*) and its seeds. It can be extracted from seed oil of natural celery, or obtained from chemical synthesis. Chinese patent 98125618. X disclosed applications of L- butylphthalide (levorotatory butylphthalide) in drugs of anti thrombosis and anti platelet aggregation, which clearly demonstrated that butylphthalide has a function of adjusting NOS-NO-cGMP system and nerve cell arachidonic acid metabolism after brain ischemia. Chinese patent 93117148.2 disclosed applications of Apigenin A in preparing of medicine for prevention and treatment of the diseases caused by brain ischemia in mammals and human. Apigenin A is in fact the non-optically active form of butylphthalide. Butylphthalide is an oily liquid with strong celery smell. The chemical structure of butylphthalide is as following:



[0003] The soft gel capsule is a relatively new form of pharmaceutical delivery system, which is especially suitable for orally delivering active ingredients in oil form. The main active ingredient is uniformly distributed in the diluting agents and the drug dosage is measured accurately in each capsule. The out surface of the capsule is smooth and round, so that the

capsule can be easily swallowed by the patient, therefore the patient compliance of the soft gel capsule is good.

Disclosure of the Invention

[0004] This invention discloses a novel butylphthalide soft gel capsule form based on our research and development on the physical and chemical characteristic of butylphthalide and utilization of the special advantage of soft gel capsule.

[0005] The purpose of the invention is to provide a butylphthalide soft gel capsule.

[0006] This invention, butylphthalide soft gel capsule, is comprised of capsule materials and drug-containing oil, in which the drug-containing oil is comprised of butylphthalide and diluent vegetable oil basically. The weight ratio between butylphthalide and diluent vegetable oil ranges from 1: 0 to 1 : 10 (w/w). Besides the main ingredients of the drug-containing oil, certain amount of antioxidant dibutyl carboxyl methyl benzene (dibutyl carboxyl toluene) can be added to the vegetable oil.

[0007] Butylphthalide in this invention means the optically inactive, mixed L and D forms of butylphthalide, and/or levorotatory optical isomer of butylphthalide, and/or dextrorotatory optical isomer of butylphthalide. Their appearances are all in the oily liquid form.

[0008] The vegetable oil can be selected from a group of oils consisting of sesame oil, corn oil, peanut oil, soybean oil, almond oil, peach kernel oil, cottonseed oil, sunflower seed oil, olive oil, or a mixture of them.

[0009] Capsule materials are basically comprised of gel materials, plasticizer and water. The composition weight ratio between gel, plasticizer and water is: 1: 0.2 to 0.4 : 0.8 to 1.3. Suitable antiseptic agents can be added to the capsule materials, such as ethyl p-hydroxybenzoate or methyl p-hydroxybenzoate.

[0010] Gel materials can be selected from one of gelatin or acacia gum (Gum Arabic), or a mixture of the two.

[0011] Plasticizer, which makes the capsule soft and elastic, can be selected from one of glycerol (glycerin) or sorbitol (sorbierite), or a mixture of the two.

[0012] In this invention butylphthalide soft gel capsule can be made by a number of conventional soft gel capsule manufacture methodologies, such as manually molding press method, rotary molding press method or dripping molding method. Usually we select press

method such as rotary molding press method. We use automatic rotary capsule molding presser, control its working temperature at 40 to 50 degree C, and ensure each molded soft gel capsule containing sufficient butylphthalide for medicinal use.

[0013] This invention chooses the soft gel capsule as a new pharmaceutical delivery form for butylphthalide, which is able to mask its characteristic strong smell. Meanwhile the new preparation, soft gel capsule, overcomes the difficulty of other oral delivery forms of delivering oily active ingredients to patients. The patients can conveniently take the oval shaped soft gel capsule orally and easily swallow them. The patients' compliance of the new delivery form preparation is good.

Modes of Carrying Out the Invention

[0014] In this invention, butylphthalide soft gel capsule is comprised of capsule materials and drug-containing oil, in which the drug-containing oil is comprised basically of butylphthalide and diluent vegetable oil. A relatively better weight ratio of butylphthalide to diluent vegetable oil ranges from 1: 1 to 1 : 8 (w/w). The further better selected weight ratio of butylphthalide to diluent vegetable oil ranges from 1: 2 to 1: 5(w/w). In the best mode, the weight ratio of butylphthalide to diluent vegetable oil is 1: 3.5(w/w). Dibutyl carboxyl methylbenzene (dibutyl carboxyl toluene) as an antioxidant with the amount of 0 to 0.2% (weight ratio) can be further added to drug-containing oil.

[0015] A better choice of vegetable oil can be selected from a group of oils consisting of peanut oil, soybean oil, corn oil, and sesame oil. The best mode choice of oil is soybean oil.

[0016] Capsule materials are basically comprised of gel, plasticizer and water. Among them, the best mode choice of gel is gelatin, the best mode choice of plasticizer is glycerol.

[0017] The following implemented experiments are given to further describe the technical scheme of this invention better. The foregoing description is intended to illustrate and not limit the scope of the invention.

Experiment 1. Preparation of butylphthalide soft gel capsules

Preparation of gelatin liquid:

[0018] Gelatin 100 grams, glycerol 30 grams, water 130 grams and 200 mg ethyl p-hydroxybenzoate.

[0019] Took gelatin and add certain amount of water, let gelatin absorb water and expend. Meanwhile, put glycerol, ethyl p-hydroxybenzoate, and the rest of the water into a colloidal sol pot, heated them to the temperature of 70 to 80 degree C, mixed them well, then added the water absorbed and expended gelatin into the pot and stirred them thoroughly till they were melted. Kept the temperature of the pot stable for 1 to 2 hours, kept the gel liquid in the pot stable and let it settle down so that the air bubbles in the gel liquid floated to the surface of it. Scraped the bubbles off the gel liquid surface. Used a piece of clean white cloth filtering the gel liquid. Kept the gel liquid temperature stable and waited for its further use. The viscosity of the gelatin liquid is usually 2.8 to 3.2 degree.

Preparation of drug-containing oil:

[0020] Weighed butylphthalide 100 grams, stirred it thoroughly and mixed it well with clear soybean oil 350 grams. The drug-containing oil was ready for use.

Press preparation of soft gel capsules :

[0021] Took prepared gelatin glycerol liquid and butylphthalide drug-containing oil and put each of them into automatic rotary molding capsule presser, controlled its working temperature at 40 to 50 degree C, pressed and produced butylphthalide soft gel capsules, each of them contains 450 mg of drug-containing oil.

[0022] The soft gel capsules press produced according to Experiment 1 method and contained Experiment 1 ratio of drug-containing oil, were in proper outside measurement sizes. The quality test result revealed that they contained uniformly distributed amount of drug-containing oil in each of the capsule. The detailed results were as follows:

Sample	Capsule 1	Capsule 2	Capsule 3	Capsule 4	Capsule 5	Capsule 6	Capsule 7	Capsule 8	Capsule 9	Capsule 10

Content (%)	99.12	98.08	100.02	99.47	99.32	101.38	98.65	98.76	99.25	98.47
Range of Content (%)	98.08 – 101.38									
Standard Deviation (%)	0.93									

Experiment 2. Preparation of butylphthalide soft gel capsules

[0023] All the rest preparing steps were the same as the steps in Example 1, except that during the preparation of drug-containing liquid steps we did not add any vegetable oil, therefore the final press produced soft gel capsules contained 100 mg drug-containing liquid in each of the capsule.

Experiment 3. Preparation of butylphthalide soft gel capsules

Preparation of gelatin liquid:

[0024] gelatin 100 grams, glycerol 40 grams, water 120 grams and 200 mg ethyl p-hydroxybenzoate. The rest preparation steps were the same as in Experiment 1.

Preparation of drug-containing oil:

[0025] Weighed butylphthalide 225 grams, stirred it thoroughly and mixed it well with clear peanut oil 225 grams. The drug-containing oil was ready for use.

Press preparation of soft gel capsules:

[0026] All the rest preparing steps were the same as the steps in above mentioned other Experiments, except that the final press produced soft gel capsules contained 200 mg drug-containing oil in each of the capsule.

[0027] The soft gel capsules press produced according to Experiment 3 method and contained Experiment 3 ratio of drug-containing oil, were tested. The test results were as follows:

Sample	Capsule 1	Capsule 2	Capsule 3	Capsule 4	Capsule 5	Capsule 6	Capsule 7	Capsule 8	Capsule 9	Capsule 10
Content (%)	98.33	96.08	99.42	101.73	94.37	100.31	92.65	98.79	102.01	95.78
Range of Content (%)	92.65 – 102.01									
Standard Deviation (%)	3.14									

Experiment 4. Preparation of butylphthalide soft gel capsules

[0028] All the rest preparing steps were the same as the steps in Experiment 1, except during the preparation of drug-containing oil steps we weighed butylphthalide 56.25 grams, stirred it thoroughly and mixed it well with clear peanut oil 393.75 grams, therefore the final press produced soft gel capsules contained 800 mg drug-containing oil in each of the capsule.

[0029] The soft gel capsules pressed according to Experiment 4 method and contained Experiment 4 ratio of drug-containing oil, were tested.

[0030] The test results are as follows:

Sample	Capsule 1	Capsule 2	Capsule 3	Capsule 4	Capsule 5	Capsule 6	Capsule 7	Capsule 8	Capsule 9	Capsule 10
Content (%)	100.03	99.08	99.42	101.73	98.57	100.31	99.55	98.99	100.11	99.98
Range of Content (%)	98.57 – 101.73									
Standard Deviation (%)	0.88									

Experiment 5. Preparation of butylphthalide soft gel capsules

Preparation of gelatin liquid:

[0031] Gelatin 100 grams, glycerol 20 grams, water 80 grams and 200 mg ethyl p-hydroxybenzoate. The rest preparation steps were the same as in Experiment 1.

Preparation of drug-containing oil:

[0032] Weighed butylphthalide 45 grams, stirred it thoroughly and mixed it well with clear peanut oil 405 grams. The drug-containing oil is ready for use.

Press preparation of soft gel capsules:

[0033] All the rest preparing steps were the same as the steps in above mentioned Experiments, except that the final press produced soft gel capsules contained 1000 mg drug-containing oil in each of the capsule.

Experiment 6. Preparation of butylphthalide soft gel capsules

[0034] All the rest preparing steps were the same as the steps in Experiment 1, except that during the preparation of drug-containing oil steps we weighed butylphthalide 90 grams, stirred it thoroughly and mixed it well with clear soybean oil 360 grams, therefore the final press produced soft gel capsules contained 500 mg drug-containing oil in each of the capsule.

Experiment 7. Preparation of butylphthalide soft gel capsules

[0035] All the rest preparing steps were the same as the steps in Experiment 1, except that during the preparation of drug-containing oil steps we weighed butylphthalide 40.91 grams, stirred it thoroughly and mixed it well with clear soybean oil 490.09 grams, therefore the final press produced soft gel capsules contain 1100 mg drug-containing oil in each of the capsule.

Experiment 8. Preparation of butylphthalide soft gel capsules

[0036] All the rest preparing steps were the same as the steps in Experiment 1, except that during the preparation of drug-containing oil steps we weighed butylphthalide 50 grams, stirred it thoroughly and mixed it well with clear soybean oil 400 grams, therefore the final press produced soft gel capsules contained 900 mg drug-containing oil in each of the capsule.

Experiment 9. Preparation of butylphthalide soft gel capsules

[0037] All the rest preparing steps were the same as the steps in Experiment 1, except that during the preparation of drug-containing oil steps we weighed butylphthalide 150 grams, stirred

it thoroughly and mixed it well with clear soybean oil 300 grams and antioxidant ethyl p-hydroxybenzoate 0.45 grams, therefore the final press produced soft gel capsules contained 300.3 mg drug-containing oil in each of the capsule.

Experiment 10. Butylphthalide content, relevant materials and disintegrating time limit assay

Assay Method

Disintegrating time limit assay

[0038] Disintegrating time limit assay was performed according to Chinese Pharmacopoeia, Edition 2000, Part Two, Appendix VA's Disintegrating Time Limit Assay.

[0039] Took samples from Experiment 1, used diluted hydrochloric acid (9 →1000) 1,000 ml as solvent, set testing temperature at 37 degree C +/- 1 degree C, set speed of raising and submerging the capsule at 30 to 32 times per minute, added baffle while testing, and observed the total disintegrating time of each soft gel capsule. The result indicated that the disintegrating time was less than 1 hour, which pass the standard of Chinese Pharmacopoeia.

Relevant materials

[0040] Relevant materials were tested according to Chinese Pharmacopoeia, Edition 2000, Part Two, Appendix VD's HPLC (High Performance Liquid Chromatography) Assay.

Assay Method

[0041] Took adequate amount of content from this product, added proper amount chloroform until it was dissolved. Added methanol up to constant volume, diluted and prepared it with methanol until its concentration was 0.5mg per 1 ml. This was the test solution.

[0042] Weighed butylphthalide adequate amount as assay control accurately, added methanol until it was dissolved, diluted and prepared it with methanol to the concentration of 15 micro gram (μg) butylphthalide per 1 ml. This was the assay control solution.

[0043] Measured assay control solution 20 micro liter (μl) accurately, ejected it into HPLC, tested it according to HPLC menu, adjusted the sensitivity of HPLC until the major composition peak measurement was 10 to 20 % of the total measurement.

[0044] Measured test solution 20 micro liter (μl) accurately, tested it the same way as testing the assay control solution on HPLC. Recorded chromatogram up to two folds of the retention time of the chromatographic measurement of the major composition peak. If impurity peaks were existed on the chromatogram, calculated the areas of every impurity peak (except the solvent peak), and the total areas of the impurity peaks should be no larger than the area of the assay control solution peak.

Content Assay

[0045] Content was tested according to Chinese Pharmacopoeia, Edition 2000, Part Two, Appendix VD's HPLC (High Performance Liquid Chromatography) Assay.

Testing of Chromatographic Condition and System Serviceability

[0046] Employed octadecyl silane bonded silica gel as filling, methanol – water (65 : 35) as flow phase, set flow rate at 1.0 ml per minute, assay wave length at 280 nm, theoretical board calculated the number of butylphthalide peaks should be no less than 1500. Butylphthalide versus impurity separation levels should be within the standard.

Control Solution Preparation

[0047] Took butylphthalide control sample about 50 mg, weighed it accurately, put it into a 50 ml graduated flask, added methanol solution to dissolve it and diluted it up to the graduated mark, mixed the solution thoroughly. Accurately measured 5 ml solution from the flask and transferred it to another 50 ml graduated flask, diluted it with methanol up to the graduated mark. This was control solution.

Assay Solution Preparation

[0048] Took adequate amount of butylphthalide content from the packages under the stock packaging difference (equivalent to about butylphthalide 50 mg), weighed it accurately, put it into a 50 ml graduated flask, added proper amount chloroform to dissolve it and proper amount of methanol to dilute it up to the graduated mark, stirred and mixed the solution thoroughly. Accurately measured 5 ml solution from the flask and transferred it to another 50 ml graduated flask, diluted it with methanol up to the graduated mark. This was test solution.

Assay Method

[0049] Measured control solution 20 micro liter (μl) and test solution 20 micro liter (μl) accurately, ejected both of them into HPLC respectively, tested them according to HPLC menu, and recorded their chromatograms respectively. Calculated the peak areas of butylphthalide ($C_{12}H_{14}O_2$) content according to external standard method, recorded the data.

The experiment data as follows:

Observation Condition		Appearance	Content (%)	Relevant Substance (%)	Disintegration Time
Environment	Time				
Initial	0 Day	Yellow transparent soft gel capsule	98.8	0.61	4'50"
Accelerated Experiment	1 month	Yellow transparent soft gel capsule	98.7	0.66	6'45"
	2 month	Yellow transparent soft gel capsule	99.3	0.63	14'10"
	3 month	Yellow transparent soft gel capsule	98.4	0.62	28'30"
	6 month	Yellow transparent soft gel capsule	99.0	0.58	49'52"
Room Temperature Control Sample	1 month	Yellow transparent soft gel capsule	98.6	0.63	5'15"
	3 month	Yellow transparent soft gel capsule	98.8	0.67	8'35"
	6 month	Yellow transparent soft gel capsule	99.4	0.66	9'45"
	12 month	Yellow transparent soft gel capsule	99.1	0.62	17'50"
	18 month	Yellow transparent soft gel capsule	98.5	0.64	27'25"
	24 month	Yellow transparent soft gel capsule	98.5	0.65	29'35"

[0050] Most soft gel capsule dosage forms suffer from the problem of product disqualification due to disintegrating time limit when the capsules pass extended shelf storage time. Even though, the test results of accelerated assay and long term assay of the present product indicate that the soft gel capsule shell ages fast and disintegrating time changes more obviously under the heated condition, the disintegrating time is less than 60 minutes. These test results meet the standard of Chinese Pharmacopoeia, Edition 2000. All the indexes of appearance, content, relevant materials of the soft gel capsule have passed the standard levels, and the product's quality is guaranteed up to 2 years.